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Promising new agents in the treatment of non-small cell lung cancer

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Abstract A number of new drugs and drug classes have recently become available for clinical testing which demonstrate significant antitumor activity in non-small cell lung cancer. The preclinical rationale, mechanism of action, toxicity profile and results of early trials of paclitaxel, docetaxel, edatrexate, CPT-11, topotecan, vinorelbine and gemcitabine in non-small cell lung cancer are reviewed.

Keywords Lung cancer · Paclitaxel · Docetaxel · CPT-11 · Topotecan · Vinorelbine · Gemcitabine

Introduction

Relatively few chemotherapeutic agents have demonstrated significant antitumor activity in non-small cell lung cancer (NSCLC). Of those agents currently available, cisplatin is generally considered to be the most important. Cisplatin is a key ingredient of combination chemotherapy for stage IV disease, and is of interest in stage III disease for both its cytoreductive and radiosensitizing potential. Cisplatin-based chemotherapy has been demonstrated to improve survival in patients with metastatic disease and is reported to be an independent prognostic variable in multivariate analysis [4]. Phase III studies in stage III NSCLC have demonstrated improved long-term survival when cisplatin-based therapy is combined with radiation versus radiation alone [27, 42, 49]. Recent trials attempting to improve results in stage III disease have focused on altering the schedule or dose of chemotherapy administered (for example, daily administration of cisplatin) or the dose schedule of irradiation (hyperfractionation) [82]. However, it is likely that additional effective chemotherapeutic agents will be required in order to improve the current level of response and survival in NSCLC.

For the first time, there are now a number of novel chemotherapeutic agents under development which show considerable promise in the treatment of NSCLC (Table 1). Each of these agents has demonstrated reproducible activity in the treatment of metastatic NSCLC. Optimally, a new agent in the therapy of NSCLC should exhibit a unique mechanism of action, a favora ble toxicity profile in comparison to standard cisplatin-based chemotherapy, significant single agent activity (i.e. > 20% activity, or > 25% improvement in median survival) and synergistic antitumor effects with cisplatin and/or radiation [40]. This review will describes the current development status of these new agents, including preclinical rationale, mechanism of action, and early clinical results. Unfortunately, in

Table 1 Promising new agents in lung cancer

Drug class	Agent	Mechanism
Taxane	Paclitaxel Docetaxel	Enhances microtubule assembly, inhibits depolymerization
Antifolate	Edatrexate	Dihydrofolate reductase inhibitor
Vinca alkaloid	Vinorelbine	Inhibits tubulin polymerization
Camptothecin	CPT-11 Topotecan	Inhibits topoisomerase I
Nucleoside analog	Gemcitabine	Inhibition of ribonucleoside reductase

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many of these early clinical studies, response rates to the new agents have been the primary endpoint reported, rather than the more important effect on survival. Nevertheless, early results are encouraging, and suggest that at least some of these new agents will eventually become part of standard chemotherapy in this disease.

Taxanes (paclitaxel and docetaxel)

Paclitaxel (taxol) and docetaxel (taxotere) are the first of a new class of antimicrotubule agents with a unique taxane ring structure and novel mechanism of action. In contrast to vinca alkaloids, these agents promote microtubule assembly and inhibit depolymerization, thereby resulting in nonfunctional microtubules [78, 83] The taxanes actually bind to the microtubule, distinguishing this agent from other antitubulin drugs such as the vincas [41]. Resistance to the taxanes is due to decreased intracellular accumulation resulting from overexpression of P-glycoprotein [41]. Another potential mechanism of resistance is an alteration in the ability of tubulin to polymerize so that the drug may actually be required for normal microtubule assembly [15]. They exhibit a broad range of preclinical antineoplastic activity, and have now been shown to have clinical activity in a number of tumor types, including NSCLC and small cell lung cancer (SCLC).

Paclitaxel

Paclitaxel is a novel diterpene plant product isolated from the bark of the Western Yew tree (Taxus brevifolia). Despite considerable early problems with drug supply, drug insolubility, hypersensitivity reactions (HSR), and even environmental impact, paclitaxel comes close to meeting the criteria for an optimal new agent. Paclitaxel possesses a unique chemical structure and mechanism of action, and demonstrates synergistic cytotoxicity with both cisplatin and radiation in vitro. In many preclinical models, cytotoxicity is schedule-dependent, with enhanced activity following prolonged exposure.

Paclitaxel also has a unique spectrum of toxicity, related in part to problems with drug solubility as well as its novel chemical structure. Paclitaxel is highly insoluble, requiring delivery in high concentrations of cremophor and resulting in a high incidence of HSR [76]. Prolonging the infusion time to 24 h and use of a steroid-containing premedication regimen has markedly reduced the incidence and severity of these reactions. Most recently, a randomized study incorporating this premedication regimen has demonstrated that the infusion time could be shortened to 3 h without an increase in HSR or loss of antitumor efficacy in ovarian cancer [91]. Other major toxicities include dose-limiting neutropenia, a dose-related peripheral sensory neuropathy, and a variety of cardiac effects Granulocyte-colony stimulating factor. (G-CSF) has proven effective in reducing the incidence of severe neutropenia and allowing paclitaxel dose escalation. However, at these higher paclitaxel dose levels, neurotoxicity has become more prominent and dose-limiting [32].

Paclitaxel has demonstrated a broad spectrum of antitumor activity in vitro and in vivo in preclinical tumor models. Early clinical studies have shown activity in recurrent ovarian cancer, breast cancer, and in both NSCLC and SCLC (Table 2) [18, 30, 64, 77]. Two studies have evaluated single-agent paclitaxel in NSCLC. The Eastern Cooperative Oncology Group (ECOG) evaluated paclitaxel 250 mg/m^2 over 24 h every 3 weeks in 24 patients with NSCLC who had not received prior chemotherapy [18]. A 21% response rate was noted. Murphy et al. evaluated 27 patients treated with paclitaxel 200 mg/m^2 over 24 h every 3 wks and noted a 24% response rate in 25 evaluable patients [64]. These two studies established a moderate but significant activity of taxol in NSCLC.

Paclitaxel and cisplatin combinations have now been evaluated clinically [32, 78]. Rowinsky et al. found that neurotoxicity was dose-limiting with a paclitaxel (250 mg/m^2) cisplatin (75 mg/m^2) and G-CSF combination [78]. Klastersky and Sculier have also studied this combination in a phase I trial without the use of hemopoietic growth factors. At a fixed dose of cisplatin of 100 mg/m^2 and paclitaxel escalating from 135 to

Table 2 Phase II trials of paclitaxel and paclitaxel-containing regimens in NSCLC (*NS* not stated, *P* paclitaxel *CBDCA* carboplatin, *G-CSF* granulocyte colony-stimulating factor, *CDDP* cisplatin)

Reference	Stage	Schedule	Evaluable	Response (%)
64	III-IV	P 200 mg/m^2 every 3 weeks	25	24
18	IV	P 250 mg/m^2 every 3 weeks	24	21
69	III-IV	P 135 mg/m^2 (24 h) CBDCA AUC = 6 every 28 days	24	22
43	III-IV	P 150–175 mg/m^2 (3 h) CBDCA AUC = 6 every 28 days	13	31
50	III-IV	P 135–215 mg/m^2 (24 h) CBDCA AUC = 7.5 every 21 days (G-CSF)	17	53
46	NS	P 135–200 mg/m^2 (3 h) CDDP 100 mg/m^2	10	50

Table 3 Phase II trials of docetaxel in NSCLC

Reference	Stage	Schedule	Prior treatment	Evaluable	Response (%)
14	"Advanced"	100 mg/m^2 every 21 days	No	9	33
			Cisplatin	11	27
17	"Advanced"	100 mg/m^2 every 21 days	No	25	32
36	III-IV	100 mg/m^2 every 21 days	No	29	38
95	"Advanced"	60 mg/m^2 every 3–4 weeks	No	84	21
34	III-IV	100 mg/m^2 every 3 weeks	No	44	33
35	III-IV	100 mg/m^2 every 3 weeks	Cisplatin	42	21
61	III-IV	75 mg/m^2 every 3 weeks	No	20	25

200 mg/m^2, there was minimal neurotoxicity; myelosuppression was the major toxicity [46]. ECOG has initiated a phase III trial comparing VP-16 (120 mg/m^2) plus cisplatin (75 mg/m^2) with paclitaxel (135 mg/m^2)/cisplatin (75 mg/m^2) and with paclitaxel (250 mg/m^2)/cisplatin (75 mg/m^2) plus G-CSF, with the aim of evaluating possible dose response effects of paclitaxel and modulation of neutropenia by G-CSF.

Combination regimens of paclitaxel and carboplatin have also been reported (Table 2) [43, 49, 69]. Principal toxicities of this combination are neutropenia (ameliorated by G-CSF) and other cytopenias. Reported response rates are in the range 22–53% with some complete responses reported. At this time it remains unclear whether these platinum paclitaxel combinations represent an improvement over currently available therapy or maximal dosing of single agent paclitaxel alone.

Docetaxel

Docetaxel is a taxane analog prepared from the needles of the European yew (*Taxus baccata*), a renewable source. Docetaxel also has improved solubility compared to paclitaxel, and is formulated in Tween-80 rather than cremophor. Docetaxel has a mechanism of action similar to paclitaxel but cytotoxicity is not schedule dependent. Docetaxel has demonstrated activity in a wide variety of preclinical tumor models and is not cross-resistant with paclitaxel in many systems [75].

Phase I trials have shown the dose-limiting toxicity to be severe but brief neutropenia [13, 92]. HSR are less severe and less common than with paclitaxel. Since the cytotoxic effects of docetaxel are not schedule dependent, this agent has most commonly been administered at doses of 80–100 mg/m^2 by a 1-h infusion, repeated every 3 weeks. Results of seven phase II trials (Table 3) [14, 17, 34–36, 61, 94] in NSCLC have shown response rates of 25–38% to single-agent docetaxel, with prolonged duration of responses. The primary toxicity seen was neutropenia; HSR were uncommon and mild. An unusual toxicity of docetaxel which may limit its usefulness is the frequent occurrence of pleural effusions (30%) and peripheral edema (60%) [35, 36]. This toxicity is seen with increasing cumulative doses and may be ameliorated with steroids [13, 38]. An intriguing finding from the study by Burris et al., is that the response rate in patients who had previous therapy with cisplatin was similar to that of chemotherapy-naive patients, raising the possibility of true non-cross-resistance with cisplatin [14]. This observation has been confirmed by Fossella et al., who demonstrated a 21% response rate with an impressive 45-week median survival in patients with platinum-refractory NSCLC [35]. It is noteworthy that this same group of investigators failed to detect activity of paclitaxel in a similar group of patients [65]. A phase I study combining docetaxel and cisplatin has been performed in advanced NSCLC [10]. Dose-limiting toxicities of neutropenia and severe diarrhea were experienced with taxotere 75 mg/m^2 and cisplatin 100 mg/m^2. No data regarding response are available.

Edatrexate (10-EdAM)

10-Ethyl-10-deaza-aminopterin (10-EdAM or edatrexate) is a recently developed analog of methotrexate designed to exploit the specificity of the N-10 position of folate for active transport and polyglutamation [88]. 10-EdAM has potential advantages over methotrexate, including increased intracellular transport, increased polyglutamation, and increased tumor selectivity and response [89]. It is synergistic with cisplatin, in contrast to methotrexate, in several murine tumor models [84]. Perez et al. have demonstrated schedule-dependent synergism of 10-EdAM with both cisplatin and carboplatin in human NSCLC cell lines [71, 72]. The toxicity profile is similar to that of methotrexate, with oral mucositis as the dose limiting toxicity and less prominent myelosuppression, diarrhea, skin rash, and mild elevation in liver function tests [47].

Table 4 reviews clinical trials of edatrexate and edatrexate-containing regimens in NSCLC [48, 52–54, 87, 90]. In a phase II trial, Kris et al. combined 10-EdAM with vinblastine-mitomycin C (EMV) at a 10-EdAM dose of 40–70 mg/m^2 per week [48]. In 99 patients with stage III and IV NSCLC, the response rate was

Table 4 Phase I-II trials of edatrexate and edatrexate-containing regimens in NSCLC, *EDX* edatrexate, *VBL* vinblastine, *CTX* cyclophosphamide, *MMC* mitomycin, *CDDP* cisplatin)

Reference	Stage	Schedule	Evaluable	Response (%)
87	III-IV	80 mg/m^2/week	19	21
52	III-IV	80 mg/m^2/week	30	10
90	III-IV	80 mg/m^2/week	45	13
48	III-IV	40–80 mg/m^2/week	20	30
		40–80 mg/m^2/week + VBL 4 mg/m^2 day 1 2 mg/m^2 day 8 4.5 mg/m^2/week + MMC 8 mg/m^2 days 1, 29, 71	99	59
53	III-IV	80 mg/m^2/week + CTX 800 mg/m^2 day 1 + CDDP 80 mg/m^2 day 1	15	46
		70 mg/m^2/week + CTX 800 mg/m^2 day 1 + CDDP 70 mg/m^2 day 1	15	27
54	III-IV	80 mg/m^2/week + CTX 800 mg/m^2/week + CDDP 80 mg/m^2 day 1 + leucovorin	14	43
31	NS	EDX 120 mg/m^2	33	60
		Paclitaxel 135–210 mg/m^2	15	20
26	NS	EDX 60 mg/m^2 day 2 Paclitaxel 110 mg/m^2 days 1, 15		

approximately 60% and the 1-year survival was 58%. A large multicenter phase III trial has recently been completed comparing EMV to MV; the final results are not yet available. Based on reported synergism of 10-EdAM with platinum compounds, a Phase II trial in NSCLC has been performed combining 10-EdAM 80 mg/m^2 days 1 and 8, cyclophosphamide 800 mg/m^2 day 1 and cisplatin 80 mg/m^2 day 1, repeated on a 21-day cycle [53]. Of 15 evaluable patients, 7 (47%) treated at this dose level responded to therapy. When chemotherapy doses were reduced due to toxicity, the response rate fell to 27%. Subsequently, the addition of leucovorin rescue in this trial was reported to reduce toxicity while preserving efficacy [54].

In a recent phase I trial in advanced solid tumors at the University of California, Davis, patients received escalating doses of 10-EdAM (60, 70, 80, 90 mg/m^2) plus carboplatin (350 mg/m^2). Mild mucositis was the most common toxicity observed and responses were noted in both NSCLC and SCLC [39]. Based on these data, the Southwest Oncology Group (SWOG) has initiated a trial of this combination in NSCLC. Two phase I trials of sequential 10-EdAM followed by paclitaxel have been reported, demonstrating both feasibility and what appears to be a high degree of activity in NSCLC [26, 31].

Vinorelbine

Vinorelbine (navelbine) is a unique vinca alkaloid in structure, selectivity of action, spectrum of activity, and toxicity profile. It is selective for mitotic microtubules versus axonal microtubules, reducing the potential for neurotoxicity compared to vincristine [9]. The structure of vinorelbine also confers a high degree of liposolubility, leading to a very long half-life and increased tissue concentrations. Vinorelbine has a very broad spectrum of preclinical antitumor activity, and is more active than other vinca alkaloids in almost all models tested [23]. At a dose schedule of 30 mg/m^2 per week, clinical activity has been shown in breast cancer, Hodgkins disease and NSCLC. Neutropenia is dose limiting.

Single agent response rates in NSCLC have been encouraging (Table 5) [7, 24, 25, 51, 94, 96]. Vinorelbine has been compared to 5FU/leucovorin in a phase III trial. This study demonstrated an advantage for vinorelbine in terms of response (12% vs 6%) and survival (29 weeks vs 21 weeks) [70]. It is unclear whether this study truly demonstrated an advantage for vinorelbine as 5FU/leucovorin has never been compared with BSC and therefore any statements as to the value of 5FU/leucovorin relative to best supportive care (BSC) are speculative. Furthermore,

Table 5 Phase II and III trials of vinorelbine and vinorelbine-containing regimens in NSCLC (*VNB* vinorelbine, *CDDP* cisplatin, *CBDCA* carboplatin, *Ifex* Ifosfamide, *G-CSF* granulocyte colony-stimulating factors

Reference	Stage	Schedule	Evaluable	Response (%)
24	I-IV "Inoperable"	30 mg/m^2/week	69	33
96	"Inoperable"	20 mg/m^2/week	19	26
		25 mg/m^2/week	18	44
	"Inoperable"	25 mg/m^2/week	69	33
51[a]	"Inoperable"	VNB 30 mg/m^2/week vs	206	14
		VNB 30 mg/m^2/week + CDDP 120 mg/m^2 every 4–6 weeks	206	28
25	III–IV	VNB 30 mg/m^2/week vs	104	17
		VNB 30 mg/m^2/week + CDDP 80 mg/m^2 every 21 days		
81	III–IV	CBDCA 350 mg/m^2 VNB 25 mg/m^2 dl, 8q 4 wks	55	36
57	III-IV	VNB 20 mg/m^2 every week × 8 Ifex 2 g/m^2 qd × 3 q28 d	18	56
62	Unresectable	VNB 25 mg/m^2 days 1, 8 every 21 days Ifex 2 gm/m^2 for 3 days every 21 days	20	40
28	III-IV	VNB 15 mg/m^2 escalating Ifex 1.6–2.0 g/m^2 G-CSF	16	50

[a] This study included a third arm of CDDP-vindesine, not shown here.

5FU/leucovorin is not generally considered an effective regimen in NSCLC and it is possible that survival may actually have been worsened in that arm.

Vinorelbine is synergistic with cisplatin in a murine model [23]. This combination has recently been tested in three separate phase III trials in NSCLC [7, 25, 51]. As shown in Table 4, the combination of vinorelbine plus cisplatin resulted in higher response rates than vinorelbine alone. Balbiani et al., in a smaller series, found no advantage to the addition of cisplatin to vinorelbine [7]. Unfortunately, study designs comparing vinorelbine alone versus vinorelbine plus cisplatin do not allow the contribution of vinorelbine to be clearly determined. Subsequently, a phase III trial comparing cisplatin alone versus vinorelbine plus cisplatin has been initiated in the SWOG. Vinorelbine has also been combined with carboplatin and with ifosfamide [8, 28, 57, 62, 81]

Camptothecins (CPT-11 and topotecan)

The camptothecins are a family of drugs derived from the oriental tree, *Camptotheca acuminata*. The original drug, camptothecin, demonstrated unacceptable bladder toxicity and a surprising lack of clinical activity despite impressive in vitro results. Two derivatives, CPT-11 (irinotecan) and topotecan, have recently entered clinical trials and may fulfil the original promise of this drug family.

Camptothecins have a novel mechanism of action, inhibition of the enzyme topoisomerase I. Topoisomerases are enzymes which allow DNA to break and reseal, thereby relieving mechanical stresses during replication and other processes which require unwinding (e.g. transcription) [12]. Camptothecins form a complex with topoisomerase I which results in DNA strand breaks and termination of transcription. Resistance to camptothecins does not appear to be related to the *MDR*1 gene.

CPT-11 (Irinotecan)

Phase I trials with CPT-11 have been completed utilizing a variety of schedules both in Japan and the United States. The dose-limiting toxicities are neutropenia and severe diarrhea which may be ameliorated with the use of high-dose loperamide [2]. Other significant toxicities for this drug are pulmonary toxicity (potentially fatal), nausea, vomiting and alopecia.

Significant clinical activity of CPT-11 has been demonstrated in phase II trials in cancers of the lung, colon, cervix, ovary, Hodgkin's and non-Hodgkin's lymphomas, acute lymphoblastic leukemia [12, 67] and NSCLC [37]. Subsequent Japanese trials have combined CPT-11 with cisplatin or cisplatin/vindesine, with response rates ranging from 40% to 54% (Table 6) [59, 63, 66, 86]. Masuda et al. utilized G-CSF to circumvent dose-limiting neutropenia, reporting a resultant 33% increase in CPT-11 dose intensity [58].

Table 6 Phase I-II CPT-11 trials of in NSCLC

Reference	Stage	Schedule	Evaluable	Response (%)
37	III-IV	100 mg/m^2/week	72	31.9
58	III-IV	CPT-11 30–70 mg/m^2 days 1, 8, 15 + CDDP 80 mg/m^2 day 1	26	54
66	III-IV	CPT-11 60 mg/m^2 days 1, 8, 15 + CDDP 80 mg/m^2 day 1	69	48
86	III-IV	CPT-11 20–100 mg/m^2 days 1, 8 every 28 days + CDDP 60–80 mg/m^2 day 1 + vindesine 3 mg/m^{2}days 1, 8	20	40
59	III-IV	CPT-11 70–90 mg/m^{2}day 1, 8, 15 + CDDP 80 mg/m^2 day 1 + G-CSF	19	42
63	III-IV	CPT-11 40–100 mg/m^2 CDDP 100–125 mg/m^2	20	45

Table 7 Phase I-II trials of gemcitabine in NSCLC (*GEM* gemcitabine, *CDDP* cisplatin)

Reference	Stage	Schedule	Evaluable	Response (%)
85	III + IV	1250 mg/m^2 every week × 3	93	20.4
33	III + IV	1000–1750 mg/m^2 every week × 3	19	21
3	III or IV	1000–1250 mg/m^2	70	20
6	III + IV	800–100 mg/m^2 days 8, 7, 14 every 28 days	79	20
74	NS	1000–2200 mg/m^2/week	20	
21	III-IV	GEM 1000 mg/m^2 every week × 3 CDDP 25–30 mg/m^2 every week	12	58
29	NS	GEM 1000 mg/m^2 every week × 3 CDDP 60–100 mg/m^2 day 15	10	60

In vitro synergy of topoisomerase I and II inhibitors has been demonstrated [5]. A phase I study combining CPT-11 and VP-16 with G-CSF support has demonstrated clinical feasibility and antitumor activity [60]. Etoposide was dosed at 80 mg/m^2 and CPT-11 was escalated to a maximum tolerated dose (MTD) of 90 mg/m^2. Dose-limiting toxicities of this combination were diarrhea and leukopenia. In NSCLC, 7 of 12 patients responded to therapy.

Topotecan

Clinical development of topotecan is presently at an earlier stage than that of CPT-11. Phase I studies have been completed, and demonstrate that neutropenia is dose-limiting. While G-CSF may ameliorate neutropenia, thrombocytopenia has emerged as the dose-limiting toxicity [80]. Importantly, the severe diarrhea syndrome described with CPT-11 has not been reported as a toxicity of topotecan. Early phase II trials in NSCLC have shown variable antitumor activity, with one study showing no activity and the other a 13.5% response rate [56, 73]. If the efficacy of this drug ultimately proves comparable to CPT-11, the favorable toxicity profile of topotecan may result in an improved therapeutic index. A phase I trial combining cisplatin and topotecan has demonstrated that toxicity is sequence dependent, but it is unclear whether increased toxicity with cisplatin followed by topotecan will result in improved antitumor efficacy [79].

Gemcitabine

Gemcitabine is an investigational antimetabolite structurally related to cytosine arabinoside (ARA-C), which functions as an inhibitor of ribonucleoside reductase. In phase I trials, the MTD has been reported to be 790–1370 mg/m^2 on a schedule of 30 min intravenous infusions weekly for 3 weeks [1]. Higher doses were achieved by prolonging infusion time. Toxicities of gemcitabine are myelosuppression, fatigue, fever and anorexia.

Preliminary results from several phase II trials in advanced NSCLC are remarkably similar (Table 7), with response rates of 20–30% [3, 6, 33, 44, 74, 85]. The

toxicity of single-agent gemcitabine in these trials was remarkably mild with approximately 5% of patients experiencing grade III or IV neutropenia. Two phase I studies of gemcitabine in combination with cisplatin in NSCLC have been reported [21, 29]. Dose-limiting toxicity was primarily hematologic. Based on the activity observed, this combination warrants further investigation.

Conclusions

For the first time since the introduction of cisplatin in the mid-1970s, a number of new chemotherapeutic agents with significant activity in NSCLC are now in development. Despite encouraging early results, the exact role that these new agents will play in the therapy of NSCLC remains unclear. Carefully designed controlled clinical trials will be required to make this determination.

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